11.   (not amended) The process of claim 1, including continuously updating and

expanding the statistically accrued evidence-based data by using the common system

template to add statistical information from patient populations from a plurality of input

55   sources.

REMARKS

This paper is filed in response to the examiner's final rejection dated January 6, 2005.

Applicant respectfully submits additional claim amendments that are distinguishable over the

prior art of record, for the reasons explained below.

As a preliminary matter, in the January 6 office action, the examiner indicated that there

was a problem with the applicant's declaration and it appears that the examiner did not receive

certain attachments to the declaration. It is respectfully believed that the attachments were

included with the applicant's declaration when it was submitted on or about September 10, 2004.

However, applicant submits a supplemental declaration herewith for the purpose of providing the

attachments. Applicant submits that the attachments address certain observations made by the

examiner on page 2 of the January 6 office action with respect to problems solved by the

invention or recognition of need for the invention.

For example, the 2003 Parade article claims that statisticians and health insurers are

spending millions to create models that predict who is at risk of a heart attack and other diseases.

The present invention accomplishes that purpose.

The May 2004 article from the Journal of Healthcare Information Management discusses

the challenges of making large amounts of data usable. This article specifically criticizes "rules-

based" systems. The prior art of record cited against applicant's claims are "rules-based"

systems. Applicant is claiming an "evidence-based" system. The difference between the two is

further explained in the following pages.

The 2004 Healthcare Informatics Online publication states that, until recently, programs

have relied on rules-based (or "threshold-based") models (*see* p. 2 of the publication). The prior

art of record cited by the examiner against the claims are "rules-based" or "threshold-based"

systems. Khorasani, in particular, is a system of this type. Once again, applicant is claiming an

"evidence-based" system (*see* below).

The examiner will also note that the applicant continues use of the claim term "a matrix"

in the application claims. The examiner objected to the September 10 amendment under

35 U.S.C. § 132, asserting that the term "a matrix" constituted new matter. Applicant has

retained that terminology and will explain below why it is not new matter. The term "matrix" is

fundamental to the mathematical technique uniquely used by the applicant, as described in the

specification, to create an evidence-based system that predicts disease outcomes on a purely

statistical model.

Applicant would like to thank the examiner for the level of clarity and detail in the

January 6 office action. The examiner will note that the remarks attached to applicant's prior

amendment explain the differences between "rules-based" and "evidence-based" systems in a

general way. Applicant continues to assert that the prior art references of record are not

"evidence-based" systems in the same way as claimed by applicant or explained here. Khorasani

states that he is "evidence-based." However, his statement, "There is a risk that the system may

reinforce bad practices by being based on assumptions about appropriateness of various

procedures," states the problem in all rules-based systems.

The problem with rules-based systems is that input variables are arbitrarily chosen and, therefore, contain bias. All three cited prior art references of record are rules/threshold-based systems, utilizing variables that are biased with respect to scope (Haessler), construction (Iliff), or selection (Khorasani).

The key functional difference between the known prior art and applicant's invention is that applicant's invention adopts an approach in which the decision making is rigorous in construction and supported by a statistical model using data that is unbiased by judgmental factors – because it is purely mathematical. As will now be discussed, the amendments submitted here add additional distinguishing language that recites limitations that are not present in the prior art of record, regardless of whether or not the examiner continues to consider them to be "evidence-based" systems.

Claim 1 now calls for a "web-based" system that is:

> "used to generate a matrix that includes a plurality of possible post-test diagnostic outcomes, each outcome indicating a possible disease and probability for that disease."[1]

It is respectfully submitted that this limitation is fully supported by the patent specification. In this respect, applicant directs the examiner's attention to page 15 of the specification which illustrates a "matrix" having a plurality of outcome alternatives – and there are other similar matrices illustrated in other parts of the specification. While it is conceded that the patent specification uses words like "table" or "custom template" in the text, rather than words like "matrix," it is respectfully submitted that a person skilled in the art, and one who is familiar with math and software development, would understand that the "tables" and diagrams

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[1] No reference cited generates a matrix that includes a plurality of post-test diagnostic outcomes. With respect to Khorasani, in particular, it generates tests that should be used to diagnose a particular disease.

shown in the specification, and the terminology "custom template" in the specification, all

describe the same thing as "matrices."

With respect to the terminology "post-test diagnostic outcomes," the examiner's attention

is directed to the following equation set forth on page 12 of the specification:

$$Post\text{-}test\ odds = pre\text{-}test\ odds\ x\ LR^2 \qquad \text{(Equation 1)}$$

"Post-test odds" can be characterized as a post-test diagnostic "outcome" or recast as a

"probability" (see below).

The invention permits a user to simultaneously display the probability of each one of a

multiple number of diseases at the same time, ranked from highest probability to lowest, or

ranked in other ways, if it is desired to do so. The probability number is created from the post-

odds number by the following equation, which is set forth on page 20 of the specification:

$$Post\text{-}test\ odds/1 + odds = probability\ of\ contribution \qquad \text{(Equation 2)}$$

Additionally, related to the equations above and the one that follows, amended claim 1

now calls for:

> "creating each post-test outcome in the matrix from an array of mathematical
> factors that are based on patient symptoms and information, with one of the
> factors being a pre-test odds factor, and with the other factors in the array being
> input as independent variables that indicate the likelihood of an outcome based on
> certain diagnostic tests."[3]

Moreover, the claim further specifies that:

> "the factors in the array are multiplied together to produce the post-test diagnostic
> outcome."[4]

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[2] The term "LR" means "likelihood ratio." "LR" and "likelihood ratio" are used interchangeably
here. How LRs are calculated is fully described in the patent specification. The use of LRs is
accepted statistical theory – although LRs have never been applied to predictive tools in the same
way as they are applied here.

[3] The prior art of record does not teach this claimed array

[4] The prior art of record does not teach multiplication of the factors in the array.

The above claim language refers to both equation 1 above and the following related

equation that is set forth on page 20 of the specification:

$$\textit{Pre-test odds x LR x LR}_2 \textit{ x LR}_3, \ldots = \textit{post-tests odds} \qquad \text{(Equation 3)}$$

Simply stated, a typical row in applicant's matrix (bear in mind a mathematical matrix

consists of rows and columns) consists of a pre-test odds number (an entry in one column of the

matrix), and a string of independent variables (each having its own column in the matrix) which,

in the preferred case, are likelihood ratios. The next number in the row (having its own entry in

a separate column) is the post-test odds number, which is an outcome (or diagnosis). The post-

test odds number is obtained by multiplying the array of other columns (or factors) together, as

per Equation 3 above. The number of independent variables is independently scalable as per

equation 3 above so that variables (or factors) can be added or removed easily as statistical

evidence grows.

Each row of the matrix is structured, mathematically, in the same way. The "pre-test

odds" number is based on prior statistical data. Each independent variable can be thought of as

an input factor. The input factors are based on data taken from the patient under examination

and act as multipliers that alter the value of the pre-test odds upwardly or downwardly, for a

particular diagnosis, depending on the quantitative value of each factor. The same input factor

can be applied against <u>all</u> of the pre-test odds corresponding to potential diseases at the same

time – which provides for upward or downward adjustment of a multiple number of outcomes at

the same time. On a rudimentary basis, this functionality is illustrated in the table below:

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Tabular Analysis for Chest Pain

Angina/CAD	0.6667 * 1.15 *1.15 * 1.15 * 1.3 * 0.7 * 1.15 * 1.3 * 2.5	77.52
GERD	0.0753 * 1.15 *1.15 * 1.15 * 1.15 * 1.15 * 0.41 * 3 * 1.15 * 3 * 1.15	42.48
Peptic Ulcer	0.0101 * 3 * 2 * 3 * 2 * 1.5	35.29
Nonreflux Esophagitis	0.0204 * 1.15 * 1.15 * 1.15 * 1.15 * 3 * 4	29.98
Tracheo bronchitis/Asthma	0.0526 * 1.15 * 1.15 * 6	29.45
Esoph Spasm	0.0309 * 1.15 *1.15 * 1.15 * 1.5 * 1.15 *1.5 * 1.15 * 1.5	17.35
Miscellaneous musculo-skeletal not chest wall	0.0204 * 1.5 * 1.5 * 3	12.1
Non-traumatic musculo-skeletal chest wall	0.0638	6
Anxiety	0.0526 * 1.15	5.7
Esoph Rupture	0.0101 * 1.15 * 1.15 * 1.15 * 1.15 * 1.5 * 1.5 * 1.5	5.62
Pneumonia	0.0417 * 1.15 * 1.15	5.22
Pericarditis	0.0204 * 1.15 * 2 * 1.15	5.12
Aortic Dissection	0.0101 * 1.15 * 1.15 * 1.15 * 1.15 * 1.5 * 1.5	3.82
Traumatic musculo-skeletal chest wall	0.0309	3
Pancreatitis	0.0101 * 1.15 * 1.15 * 2	2.6
Mitral Valve Prolapse	0.0101 * 1.5 * 1.5	2.22
Superficial lesions	0.0204	2
Pulmonary Thromboembolism	0.0101 * 1.15 * 1.15 * 1.15	1.51
Pneumothorax	0.0101 * 1.15 * 1.15	1.31
Shingles	0.0101 * 1.15	1.14

Referring to the above table with a matrix in mind, the top row corresponds to the diagnosis or outcome, "Angina." The table reflects a "20 row" matrix, each row corresponding to a different disease. Bear in mind that the number of rows are "infinitely scalable," which means new rows can be added, corresponding to additional diseases, or deleted. Likewise, columns are also infinitely scalable, depending on the number of input factors.

The above table is representative of how the invention outputs information to the user (a doctor, for example) based on data input from the patient. The examiner's attention is directed to the line that indicates "pneumonia" as a possible diagnosis for a patient who enters a hospital complaining of chest pain. According to the above table, any patient walking into a hospital complaining of chest pain (prior to being subjected to any diagnostic tests) has pre-test odds of 0.0417 for pneumonia (whereas pre-test odds for angina are 0.667). There are two independent variables associated with pneumonia in the table illustrated above (which was taken from the beta version of the invention), each one being equal to 1.15, each one being related to the patient's answer to a question or a test result. According to the patent specification, these variables are determined by using statistical likelihood ratios.

One way to think of a likelihood ratio is that it takes into account that test results are not absolute. In other words, as a simplistic example, a person might test positive for use of opiates, but the positive test does not conclusively establish drug use – because a positive test could also result if the person had eaten a poppy seed muffin. So, a likelihood ratio indicates the likelihood that a "positive" test means that the person actually has the thing that is being test for – *i.e.*, the disease. Some tests are more definitive than others – which alters the magnitude of the likelihood ratio upwardly or downwardly and, consequently, the probability of various diseases or outcomes.

Applying this explanation to the pneumonia row in the above table, the first input variable, 1.15, in the pneumonia "row," is essentially a numerical factor that increases the odds that the patient has pneumonia as a result of a patient test. The second variable (also 1.15) similarly increases the odds, but from another test applied to the same patient. When the pre-test odds are multiplied by these two variables (.0417 x 1.15 x 1.15), it creates a post-odds product equal to .055 (Equation 3) or a 5.22% probability (Equation 2). As will be further explained below, an independent variable can be created every time a question is asked or a test conducted.

One of the utilitarian aspects of the invention is that it is very easy to adapt to changes – whether changes come in the form of new tests that are developed by those in the medical profession or old tests that are discarded. For example, the particular tests that gave rise to one of the 1.15 factors could be discarded if the medical community eventually concludes that it is not a viable test. An advantage of the invention is that it would be easy to remove that factor from the applicable matrix without having to reprogram the entire system. At a much, much higher level of understanding, it is possible that independent variables will be self-correcting. In other words, the statistical accrual of data that gives rise to the calculation of each independent variable may indicate that a particular "positive" test for a particular disease does not mean anything one way or the other, in which case, the independent variable would approach 1.0 (if likelihood ratios are used) and therefore would not alter the pre-test odds at all. In fact, in actual use, many likelihood ratios will indeed have a value of "1," or very close to "1," because they are essentially "insensitive" to the prediction of a particular disease, one way or the other. Stating it another way, certain questions are essentially statistically meaningless as indicators for certain diseases.

If one visualizes a mathematical matrix and applies it to the above table, the "pre-test odds" numbers make up one column in the matrix (having 20 rows). The likelihood ratios are entered in other columns, and the post-test odds (converted to a probability) is in the final column on the right. As mentioned above, the array of pre-test odds and likelihood ratios are multiplied, according to Equation 3 above, to generate the post-test number. This feature is now a claimed limitation and, once again, is not present in the prior art of record.

A superficial similarity between the invention disclosed here and the rules-based systems in the prior art is that both systems produce diagnostic results by conducting an inquiry of the patient – which is based on answers to questions or test results. The functional difference is this: a rules-based system begins with a question. Depending on the answer, it leads to one or another question, which leads to ever-branching logical paths and loops until the result (that is, the most likely diagnosis) is obtained. With respect to the prior art, Haessler utilizes "selected branchpaths," Iliff utilizes "binary trees," and Khorasani utlizies "menus," which are all examples of branchtree logic and therefore rules-based systems.

With the present invention, and visualizing the table discussed above once again, before the first question is asked, the only numerical factors that apply are the pre-test odds (in the first column). When the first question is asked, it generates a likelihood ratio ("LR") for each possible disease listed on the matrix. The LR is meaningful for some potential diagnoses (and therefore creates a numerical factor to be multiplied against the pre-test odds number) and not meaningful to others (mathematically, the LR would equal "1," as stated above, and therefore does not impact the pre-test odds of a different diagnosis). A separate LR for each disease on the

matrix is generated based on a single question – essentially filling one column for 20 rows.[5] As a practical matter, some LRs may alter the pre-test odds for some diseases (1.15 for pneumonia in the above example), some may not (an LR equal to "1" – which means the answer to a question or test means nothing with respect to that disease). But a single question asked of a patient also has the potential of altering all of the pre-test odds.

As a consequence, each question alters all of the potential results at the same time, and it occurs again and again refining accuracy, every time a question is asked. The final post-test probability for all the possible outcomes (*i.e.*, possible diseases) is reached simultaneously in parallel fashion. Reaching the final probability in a rules-based system is more serial-based, because it is based on the branch-tree logic of an "if-then" approach.

The term "rules-based" once again applies to Khorasani in that "if" a study is not available, a physician is sent back to the "reason/indication"menu (column 5, lines 47-52).
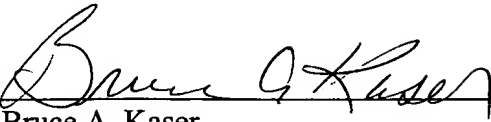
The array that is described above, and which is now set forth in the claims, is unique to the application of a web-based medical diagnostic systems. It is respectfully submitted that claim 1 is allowable for this reason. While amendments have been submitted for the remaining dependent claims as well, these amendments are largely made for the purpose of making their language consistent with amended claim 1. Applicant continues to assert that dependent claims 8-11 are independently allowable because they set forth limitations that are not present in the prior art of record.

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[5] The table does not depict LRs having a "1" value because they are washed out from the equation or multiplication of each array in each area.

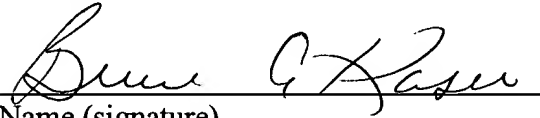Applicant respectfully requests a brief interview to discuss the above.

Respectfully submitted,

VICTOR LEVY

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I, Bruce A. Kaser, hereby certify that this document and its attachments are being deposited with the U.S. Postal Service as First Class Mail, postage prepaid, in an envelope addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 7th day of March, 2005.

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Name (signature)